UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/623,728	01/22/2001	Habib Zaghouani	027607-000212US	6688

87008 7590 07/24/2009

MultiCell Technologies, Inc.
c/o David Lewis
1250 Aviation Avenue, Suite 200B
San Jose, CA 95110

EXAMINER	
SZPERKA, MICHAEL EDWARD	

ART UNIT	PAPER NUMBER
1644	

MAIL DATE	DELIVERY MODE
07/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/623,728	ZAGHOUANI, HABIB	
	Examiner	Art Unit	
	Michael Szperka	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 17, 2009 has been entered.

Applicant's response and amendments received May 17, 2009 are acknowledged.

Claims 8-28 have been canceled.
Claims 1 and 4-7 have been amended.
Claims 1-7 are pending in this application.

Claims 1-7 are under examination as they read on fusion proteins comprising the peptides of SEQ ID NOs:1 and 2.

Specification

2. Applicant's amendment to the specification received May 17, 2009 are acknowledged and accepted. Note that the underlining in the replacement text DOES NOT indicate new text but merely serves to focus the reader's attention upon two resides within the longer amino acid sequence in accordance with the text of this paragraph as originally filed. The underlining is not new matter and does not in any way add new text; rather the underlining is for formatting purposes only.

Claim Objections

3. The objection to claim 1 has been obviated by applicant's claim amendments received May 17, 2009.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-7 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for the reasons of record.

The office action mailed November 17, 2008 states:

> Applicant has amended the claims to recite a fusion product comprising SEQ ID NOs:1 and/or 2 that alleviates symptoms associated with multiple sclerosis (MS). On page 27 of the specification, PLP1 is defined as a peptide fragment of proteolipid protein (PLP) comprising amino acid residues 139-151, while PLP-LR is a peptide analog of PLP1 which does not activate PLP1 pulsed cells. Example 1 on page 28 discloses that PLP1 is SEQ ID NO:1, which is HSLGKWLGHPNKF. This example further discloses that PLP-LR is SEQ ID NO:2 which is HSLGK*LLGR*PNKF (mutations from PLP1 in italics). These two peptides were then used to construct immunoglobulin molecules comprising proteolipid peptides in place of the heavy chain CDRs, with the resulting molecules being designated as Ig-PLP1 and Ig-PLP-LR. Ig-PLP1 and Ig-PLP-LR were administered to mice in examples X-XXV. Some of these examples appear to indicate that Ig-PLP1 and Ig-PLP-LR may inhibit the development of EAE, a mouse model that mimics some of the signs and symptoms of MS, if the molecules are administered at birth (example XIX), and that aggregated forms of the molecules may have therapeutic efficacy at later timepoints (example XXV).
>
> However, peer-reviewed publications also discuss the administration of Ig-PLP1 and Ig-PLP-LR, such as Legge et al. (1997 and 1998, see entire documents). These non-patent disclosures indicate that the sequences of the PLP1 and PLP-LR peptides as being HSLGKWLGHPDKF and HSLGK*LLGR*PDKF respectively (differences from SEQ ID NOs:1 and 2 underlined). Amino acids 139-151 of mouse PLP are HSLGKWLGHPDKF (Kuchroo et al., see particularly the abstract). Human PLP is HCLGKWLGHPDKF (see enclosed sequence alignment). As such, human and murine wild type sequences comprise a D, rather than an N residue at the position corresponding to aa 149. Inspection of the figures disclosed by Legge et al. in their 1998 paper reveals them to bear striking similarities to those of the instant specification (for example, compare Figures 11 and 12 of the instant specification with Figures 2 and 3 of Legge et al.). Given that the peer-review data and the data of the instant specification appear to be similar and use fusion proteins identified by identical names, it is unclear if the fusion proteins disclosed in the instant specification are or are not the same as those disclosed in the peer reviewed literature. This issue is important because it appears that SEQ ID NO:1 and SEQ ID NO:2 are not naturally occurring sequences, and it appears that these sequences are not disclosed anywhere else excepting the instant specification and other patent applications that ultimately claim priority to the application which has issued as patent 6,737,057.
>
> Thus, while no mechanism of action is recited for how the claimed fusion proteins alleviate MS symptoms, based upon the specification it appears that the peptides recited as being part of the claimed fusion proteins are required to induce tolerance to an altered self-peptide

(since SEQ ID NOs:1 and 2 are not naturally occurring as discussed above) to treat the autoimmune disease MS. Tolerance-inducing peptide immunotherapy is well known in the immunological arts. In some cases significant results have been demonstrated in in-bred small animal models. However, said results have not been repeated in human trials. See for example, *Marketletter* (9/13/99) which teaches the complete failure in human trials of two peptides designed for tolerance induction. Both Myloral (for MS) and Colloral (for rheumatoid arthritis, RA) provided successful results in rodent models (EAE and collagen induced arthritis, respectively) but were unsuccessful in human applications.

As set forth above, the references demonstrate that even unsubstituted peptides (peptides that are not APLs, which SEQ ID NOs:1 and 2 are since they are non-naturally occurring sequences) that work in *in vivo* small animal disease models cannot be expected to work in humans. Regarding the even more unpredictable APLs, Anderton (2001), teaches that:

> "This unpredictability [of APLs] led us to argue against the use of antagonist or immune deviating APL in human autoimmune disorders" (page 370).

Indeed, the reference goes on to teach that APL administration to humans can be dangerous and that in at least one case a human trial was suspended due to adverse reactions in a significant number of patients.

Other investigators have discussed additional problems in establishing human tolerance. See, for example, Dong et al. (1999):

> "Despite the fact that it has been relatively easy to induce true tolerance in small experimental animals, translating these studies into larger animals and humans has been much more difficult to achieve. Some of the hurdles that may explain this dilemma are summarized in Table 3. *Even if we have the ideal strategy to use in humans, the lack of reliable predictable assays for rejection or tolerance still does not allow us to know if a patient is truly tolerant so that immunosuppressive agents may be withdrawn"* (emphasis added).

A review of the instant specification reveals that a T cell response to PLP-1 can be inhibited in the experimental mouse model of EAE. As set forth above, experimental results in an EAE have failed to translate into effective treatments for autoimmune diseases, and the claimed fusion protein is recited as alleviating symptoms associated with multiple sclerosis.

Further, Applicant's subsequent work indicates that the claimed products do not necessarily comprise the recited functional attributes. See for example Legge et al. (1998). Therein the authors teach that APLs function as "T cell antagonists, partial agonists, or super agonists" (page 106). The authors go on to teach that PLP-LR stimulated PLP1 specific T cells (paragraph spanning page 109 and 110), i.e., the T cells that would be pathogenic in an MS patient and thus cause exacerbation, rather than amelioration of disease symptoms. Thus, the recited products are reasonably expected not to comprise the recited biological activity.

A set forth in *Rasmusson v. SmithKline Beecham Corp.,* 75 USPQ2d 1297, 1302 (CAFC 2005), enablement cannot be established unless one skilled in the art "would accept without question" an Applicant's statements regarding an invention, particularly in the absence of evidence regarding the effect of a claimed invention. Specifically:

> "As we have explained, we have required a greater measure of proof, and for good reason. If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the "inventor" would be rewarded the spoils instead of the party who

> demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing an unproved hypothesis."
>
> Even more recent work supports the rejection for lack of enablement. A review by Steinman (2007) teaches that, while antigen-specific immunosuppression would be desirable, it has generally failed in humans. In trials with even the most well studied MS-related antigen, myelin basic protein 83-98 (MBP83-98) in some instances administration of the antigen exacerbated disease and in other instances caused such severe hypersensitivity reactions that the trials had to be terminated prematurely (page 663). The Inventor's own work, Bell et al. (2008) further demonstrates that the claimed product may not comprise the recited biological activity. The reference teaches that administration of Ig-PLP1 exacerbated EAE in certain F1 mice (generated to more closely model the outbred human population). As the Inventor concluded, "complex polymorphisms which could result in unbalanced MHC expression need to be taken into consideration to devise effective Ag-specific therapy against the disease". The instant application has a priority date of 1997, yet even presently it is not clear that the products claimed by applicant would actually serve to alleviate MS symptoms since many promising reagents identified in the EAE model have not been successfully applied to the human disease MS and because products that appear to be structurally related to those claimed by applicant appear to have exacerbated, rather than ameliorated, EAE in some mice. Note that all currently pending claims ultimately depend from claim 1 and thus all claimed products must comprise the ability to alleviate symptoms of MS.
>
> Thus, in view of the quantity of experimentation necessary, the lack of sufficient guidance in the specification, the lack of working examples specific for human disease the unpredictability of the art, and the breadth of the claims, it would take undue experimentation to make and use the instant claimed products.

Applicant's arguments filed May 17, 2009 have been fully considered but they are not persuasive. Applicant has argued that by deleting “for the alleviation of symptoms associated with multiple sclerosis” applicant has obviated the issues of record and that the claims as presently recited are fully enabled and are in condition for allowance.

This argument is not persuasive. While applicant has deleted the intended use limitation of alleviating multiple sclerosis symptoms, the independent claim still recites “thereby resulting in downregulation of autoreactive T cells”. Legge et al. disclose data that Ig-PLP-1 is an activator of T cells in vivo (J. Exp. Med, '97, of record, see entire document, particularly figure 7). Also, Bell et al. (of record) disclose that in F1 mice, Ig-PLP-1 induces T cells which produce IL-5, leading to the exacerbation of autoimmune disease. As such, experimental data indicates that the claimed products potentiate T cells responses and augment autoimmune disease, in contrast to the recited functional limitation of "downregulating autoreactive T cells". Note that an autoreactive T cell is one which is stimulated by a peptide epitope of a self antigen presented in the context of an appropriate MHC molecule. When Legge et al. administered Ig-PLP-1 to mice,

they observed a T cell response specific for the self antigen peptide of PLP-1. Since these elicited T cells respond to a self peptide epitope they are by definition autoreactive. Further, as discussed in the rejection of record, the peptides of SEQ ID NOs:1 and 2 are altered peptide ligands since these peptides are not simple truncations of either mouse or human PLP, and the use of altered peptide ligands as reagents to downregulate autoreactive T cells and thus treat the underlying autoimmune disease, is not predictable as evidenced by the teachings of Anderton (of record). Applicant has not addressed this aspect of the rejection of record in the response received May 17, 2009. The rejection is maintained.

6. No claims are allowable.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael Szperka whose telephone number is (571)272-2934. The examiner can normally be reached on M-F 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on 571-272-0735. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Michael Szperka, Ph.D.
Primary Examiner
Art Unit 1644

/Michael Szperka/
Primary Examiner, Art Unit 1644